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Foods and food constituents, acute effects on human behavior

Harris R. Lieberman

Scientific and popular interest in the effects of nutrients, food constituents, and nutritional supplements on the brain and behavior has been growing dramatically. The use of products sold as dietary supplements in the United States has become a multibillion-dollar industry. This growth can be attributed in part to a federal law passed in 1994, the Dietary Supplement Health and Education Act (DSHEA), deregulating the sale of nutritional supplements, as well as a wide variety of other, naturally occurring compounds. Before DSHEA, the sale of supplements in the United States was highly regulated, and relatively few products were widely available. Now a whole range of dietary supplements, including many that are purported to affect the brain, can be purchased in virtually every pharmacy and supermarket in the United States. The more popular supplements claimed to affect CNS functions include the following: individual amino acids; herbal products such as ginkgo biloba, St. John's wort, kava kava and ginseng; weight loss products, which often include ephedrine and caffeine; melatonin; antioxidants; and various vitamins and minerals.

This article is focused on food constituents as opposed to dietary supplements, the distinction being that many so-called dietary supplements, as defined by DSHEA, are not naturally present in foods; for example, melatonin, ginkgo biloba, ephedrine, St. John's wort, and kava kava. Many of these naturally occurring products would be classified as drugs if conventional, pre-DSHEA criteria were used. In fact, pure ephedrine is defined as a drug in the United States, but when the same compound is naturally present in an herbal product, it is classified as a dietary supplement. For legal and regulatory purposes, the definition of a *dietary supplement* in the United States, as defined by DSHEA, is extraordinarily broad. In many other countries, and from a purely scientific perspective, many of the products that were deregulated by DSHEA are not dietary supplements.

Our focus is further specified to food constituents that may have acute behavioral effects, including macronutrients such as carbohydrate and protein, caffeine, and certain amino acids. A large, coherent body of scientific literature on the effects of foods and specific food constituents on human cognitive function does not exist. Parametric studies to examine the behavioral effects of long-term consumption of particular diets varying in macronutrient content (protein, carbohydrate, and fat) have not been conducted. Unfortunately, this does not prevent many lay publications, especially books advocating particular diets, from making a broad range of unsubstantiated behavioral claims.

Much of the research on the behavioral effect of foods has focused on foods or food components that are likely to have acute effects on brain function. At least three food constituents have been evaluated for acute behavioral effects on humans in controlled studies:

- (1) Certain amino acids, notably tryptophan and tyrosine, which are the precursors of specific brain neurotransmitters
- (2) Protein foods relative to carbohydrate foods
- (3) Caffeine

Each of these foods will be individually discussed below. We will not discuss effects of changes in energy supply on behavior, such as in studies conducted with meals that do not provide adequate energy (caloric restriction) or studies on the acute effects of energy supplementation (such as glucose).

1. Amino acid neurotransmitter precursors

Certain large neutral amino acids (LNAA) found in protein-containing foods are precursors of important brain neurotransmitters. These amino acids are transported across the blood-brain barrier. One of these is tryptophan, the precursor of the neurotransmitter serotonin. When tryptophan is administered systemically in pure form it can increase brain tryptophan and serotonin levels. This amino acid has been reported to affect normal human mood, sleep, and pain sensitivity. Carbohydrate foods, although they may contain little tryptophan, paradoxically can also increase brain tryptophan and serotonin (see discussion below). Tyrosine, another LNAA, is the precursor of dopamine and norepinephrine, and under certain conditions, such as exposure to various forms of stress, its availability can affect the synthesis of these neurotransmitters. Tyrosine may affect behaviors associated with these catecholamine neurotransmitter systems, such as motor activity, mood-state, and the behavioral response to acute stress.

There is little doubt that tryptophan, when it is administered in sufficient quantities, has sedative-hypnotic properties. Many investigators have demonstrated effects of tryptophan on human alertness, as measured by self-report mood questionnaires and on latency to fall asleep as measured by polysomnography (EEG). The hypnotic-like effects observed in humans after tryptophan administration are consistent with reports implicating brain serotonin neurons in the regulation of alertness since tryptophan can increase brain serotonin levels in animals. Although tryptophan is clearly not as potent as prescription hypnotic drugs, it was sold in many health food stores as a natural sleep aid until 1989. It was withdrawn from the market when a large number of cases of a rare disease called eosinophilia-myalgia syndrome (EMS) were seen in some individuals who were taking it. The exact cause of the disease has never been conclusively demonstrated, but most of the experts in the field agree that contaminated tryptophan was accidentally produced and sold by one company.

The dose of pure tryptophan required to induce drowsiness probably produces changes in brain tryptophan that are somewhat larger than those produced by any naturally occurring food. Therefore, although tryptophan is a common food constituent, it may have to be given in pure form, not as a food, for it to have sedative-like properties. However, the minimal change in brain tryptophan concentration that must be elicited to modify behavior has not been definitively established and is a matter of some controversy. The effects of foods such as carbohydrate or protein that alter brain tryptophan and serotonin concentration are more difficult to demonstrate and will be discussed in the next section.

Tyrosine is another LNA and neurotransmitter precursor that can, under certain conditions, affect brain neurotransmission. Tyrosine is the precursor of dopamine, norepinephrine, and epinephrine, and these catecholamines are central neurotransmitters. It has been shown that when central catecholaminergic neurons fire frequently, as can occur in certain disease states and during exposure to acute stress, they become precursor-sensitive. Although these neurons are not believed to be affected by the availability of their precursor normally, when they are firing frequently, they may require additional tyrosine to function optimally. It has therefore been suggested that the availability of greater-than-normal levels of tyrosine may prevent some adverse effects of acute stress since central noradrenergic neurons seem critical for regulating key behavioral parameters such as attention, arousal level, and mood state. It is well documented that acute exposure to many stressors increases brain catecholamine release, especially norepinephrine.

To examine the hypothesis that supplemental tyrosine can prevent some adverse effects of acute stressors, a number of studies have been conducted to evaluate the effects of orally administered tyrosine on normal humans exposed to various types of acute stress. To date, tyrosine has been found to have positive effects on cognitive performance in humans exposed to stressors such as cold, high altitude, and psychologic stress. Functions such as reaction time, vigilance, learning, and memory improved when tyrosine was administered during exposure to acute stress. These human studies are consistent with behavioral and neurochemical studies of animals that demonstrate tyrosine has beneficial effects on the ability to cope with acute stress and improves performance on tasks requiring attention and learning.

2. Protein foods and carbohydrate foods

Although the behavioral effects of protein versus carbohydrate meals are controversial, it is clear that feeding humans and animals protein, as opposed to carbohydrate, has opposite effects on brain tryptophan and its neurotransmitter product serotonin. Because tryptophan is present in protein, but not carbohydrate foods, one might assume ingestion of protein would elevate tryptophan in the plasma and brain. However this is not the case. Protein meals do elevate plasma levels of tryptophan, but tryptophan competes with all the other LNAAs, at the blood-brain barrier, for access to the brain. Therefore the parameter determining tryptophan's access to the brain is the ratio of its plasma concentration to the other LNAAs, not its absolute plasma concentration. Since tryptophan is the rarest of the LNAAs with regard to its concentration in protein foods, its plasma ratio (as opposed to concentration) declines after such foods are ingested. Protein meals therefore decrease plasma tryptophan ratio, and less tryptophan enters the brain and is available for serotonin synthesis.

It might also be anticipated that a pure carbohydrate meal would have little effect on plasma tryptophan concentration since this amino acid is not present in such foods. However, carbohydrate meals do significantly affect the ratio of plasma tryptophan to the other LNAAs, because of the secretion of insulin such meals elicit. Insulin lowers the plasma levels of the other LNAAs relative to tryptophan, because the other LNAAs are transported into skeletal muscle. Therefore carbohydrate meals have an effect opposite to that of protein meals on plasma tryptophan ratio—they increase the tryptophan/LNAA ratio, regardless of the type of carbohydrate administered (Figure 1). Consequently, more tryptophan is available for transport into the brain, and carbohydrate meals increase brain serotonin. The effect of a carbohydrate meal therefore resembles, with regard to changes that occur in plasma LNAAs, administration of pure tryptophan, whereas a protein meal may decrease brain tryptophan.

Because carbohydrate meals increase brain serotonin and protein meals have the opposite effect, it might be predicted that these foods would also have opposite effects on performance and mood. Since pure tryptophan has sedative-like properties, one would predict that carbohydrate foods, compared with protein foods, would increase sleepiness. Several studies have been conducted to test this hypothesis, and although they suggest that in some instances carbohydrate meals may increase sleepiness compared with protein meals, the results are not definitive. Other studies indicate that regardless of its composition, a large meal at lunchtime will increase sleepiness. Furthermore, some investigators have observed that glucose and carbohydrate beverages enhance certain aspects of cognitive functioning, especially memory and vigilance. The confusing and contradictory results of behavioral studies on macronutrients are probably due to differences in experimental design, behavioral tests employed, and control procedures at different laboratories.

3. Caffeine

One common food constituent that clearly affects behavior is caffeine. About three-quarters of the caffeine ingested in the United States is consumed in coffee. However, the caffeine content of this beverage varies greatly depending on the type of coffee bean used and the method of brewing. Of the types of coffee regularly consumed in the United States, drip-method coffee usually contains the highest amounts of caffeine, often over 100 mg per cup, whereas instant coffee tends to contain the least, about 60 mg per cup (Table 1). A variety of other products also contain caffeine, such as tea, cola beverages, and some other soft drinks, as well as chocolate. A typical serving (12 oz) of a cola beverage contains about 40 mg of caffeine (Table 1 and Table 2).

Classically, caffeine, a xanthine, has been considered to have stimulant-like effects on behavior. These effects are believed to be mediated via central adenosine receptors. Adenosine appears to be an inhibitory neuromodulator, and caffeine is a potent blocker of the effects of endogenous brain adenosine.

Caffeine clearly has behavioral effects at high doses and when individuals are sleep-deprived. It is more difficult to show its effects at the lower doses found in single servings of common foods with individuals who are not sleep-deprived. However, low and moderate doses of caffeine, equivalent to single servings of coffee, tea, and cola beverages can increase the ability of humans to maintain vigilance and may improve other aspects of performance as well, even in well-rested volunteers. Vigilance is the ability to focus attention to the task at hand for long periods of time. Operating motor vehicles and monitoring automated equipment are examples of real world tasks that require vigilance. Studies conducted in automobile simulators have shown that driving performance is significantly improved by caffeine administration in rested and sleep-deprived volunteers. Therefore, the use of moderate doses of caffeine may prevent the types of lapses in attention that can lead to accidents. Caffeine's effects on cognitive performance appear to generalize to a greater variety of cognitive functions when it is administered to sleep-deprived individuals, whose cognitive performance is already significantly degraded. High doses of caffeine, equivalent to four or more cups of coffee, especially in individuals who rarely use it, may have adverse effects on mood and performance. Also, when suddenly deprived of caffeine, individuals who are regular consumers sometimes experience headache and malaise and their cognitive performance may be adversely affected.

4. Conclusion

Detecting the effects of food constituents on behavior is difficult, due in part to the subtlety of the effects and the lack of standardized and sensitive tests of human mood and performance. However, when sufficient doses of the amino acid tryptophan are administered, sedative-like effects can be observed. In addition, it appears that administration of tyrosine may reduce some of the adverse behavioral effects of exposure to acute stress. Caffeine clearly improves vigilance, and its effects seem to generalize to other cognitive functions when individuals are sleep-deprived.

5. Acknowledgments

Approved for public release; distribution is unlimited. The views, opinions, and/or findings in this report are those of the authors and should not be construed as an official Department of the Army position, policy or decision, unless so designated by other official documentation. Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on the use of volunteers in research. For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law CFR 46. Citation of commercial organization and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations

6. See also

Appetite or body weight regulation and their disorders

Body weight regulation: the ponderostat

Eating disorders

Serotonin

Xanthines: caffeine and theophylline

Feeding: control of eating

Neurotransmitters

Tryptophan

Tyrosine

Sleep: behavior and cellular mechanisms

Mental illness, nutrition and

7. Further reading

Bellisle F, Blundell JE, Dye L, Fantino M, et al. (1998): Functional food science and behaviour and psychological functions. *Brit J Nutr* 80, S173-S193

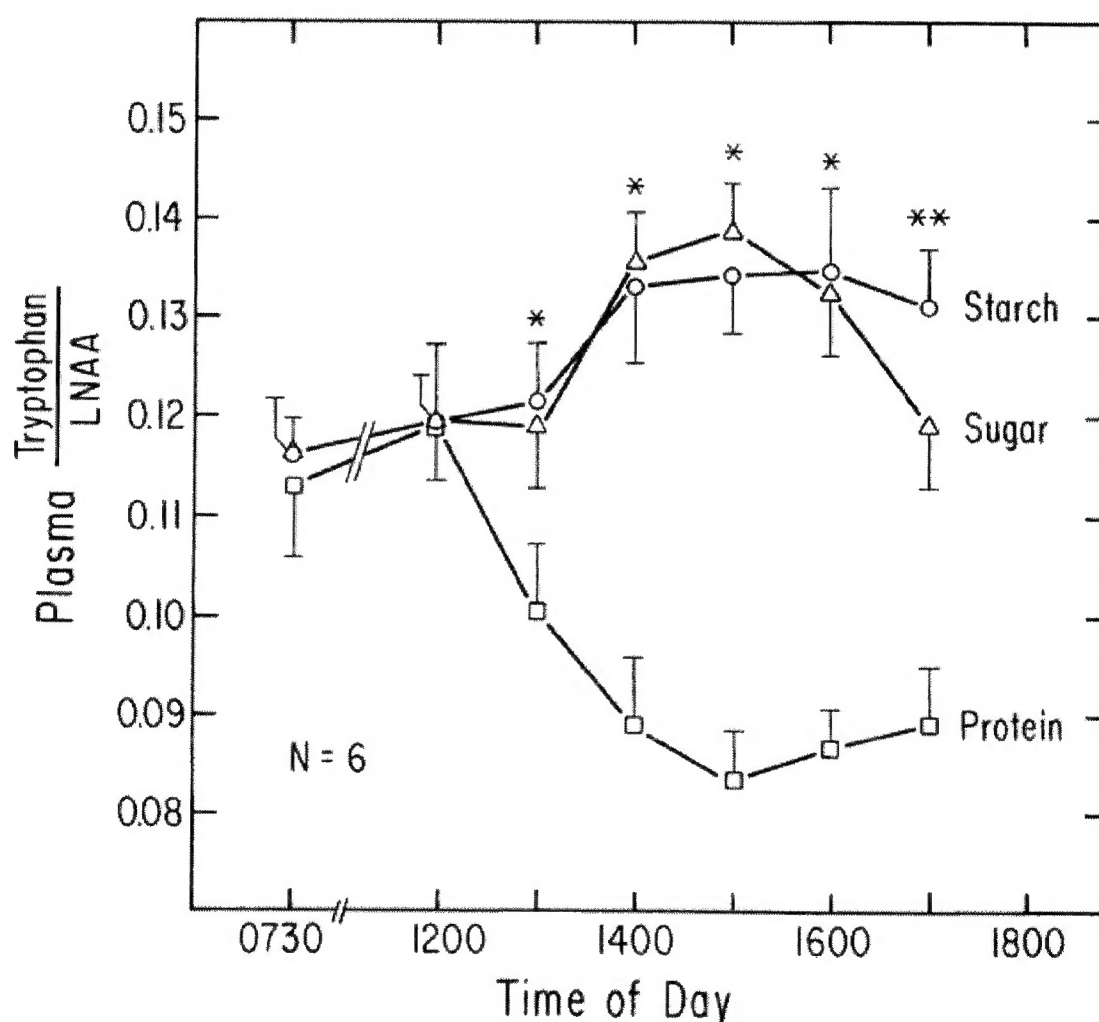
Lieberman HR (2001): The Effects of ginseng, ephedrine and caffeine on cognitive performance, mood and energy. *Nutr Rev* 59(4):91-102

Lieberman HR (1992): Caffeine. In: *Factors Affecting Human Performance, Vol. II: The Physical Environment*, Jones D, Smith A, eds. London: Academic Press

Lieberman HR (1994): Tyrosine and stress: human and Animal studies. In: *Food Components to Enhance Performance*, Marriott B, ed. Washington, DC: National Academy Press, pp. 277-299

Lieberman HR, Falco CM, Slade SS (2002): Carbohydrate administration during a day of sustained aerobic activity improves vigilance, assessed with a novel ambulatory monitoring device, and mood. *Am J Clin Nutr* 76:120-127

Wurtman RJ, Hefti F, Melamed E (1981): Precursor control of neurotransmitter synthesis. *Pharm Rev* 32, 315-335



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Figure 1. The effects of isocaloric lunch meals on human plasma tryptophan to other LNAAs ratios. The ratio is an index of brain tryptophan influx and is related to brain serotonin synthesis. The meals contained either 120 g of starch (circle), 120 g of sucrose (triangle), or 80 g of animal protein (square) and were administered at 1200. An * indicates $p < .01$ difference between protein and the other meals, and ** indicates $p < .05$ between all meals.

Table 1. Estimated caffeine content of selected beverages and foods

Item	Caffeine content* (mg)
Coffee (5-oz cup)	
Drip method	90-150
Percolated	64-124
Instant	40-108
Decaffeinated	2-5
Instant decaffeinated	2-3
Tea, loose or bags (5-oz cup)	
1-min brew	9-33
3-min brew	20-46
5-min brew	20-50
Tea products	
Instant (5-oz cup)	12-28
Iced tea (12-oz can)	22-36
Chocolate products	
Hot cocoa (6 oz)	2-8
Dry cocoa (1 oz)	6
Milk chocolate (1 oz)	1-15
Baking chocolate (1 oz)	35
Sweet dark chocolate (1 oz)	5-35
Chocolate milk (8 oz)	2-7
Chocolate-flavored syrup (2 tbsp)	4
Cola beverages (12-oz serving)	
Coca-Cola Classic™	46
Pepsi™	38
Coke™	46
RC Cola™	36
Diet Pepsi™	37
Diet Coke™	46
Diet RC Cola™	36
TAB™	47
Jolt™	71
Other soft drinks	
Dr. Pepper™	40
Diet Dr. Pepper™	41
Mountain Dew™	55
Mellow Yellow™	52
Diet Mellow Yellow™	12
Mr. Pibb™	41

*Institute of Food Technologists Expert Panel (1987); Consumer Reports (1991); Lieberman (1992); Barone and Roberts (1996); Pennington (1998)

Table 2. Barone and Roberts' standard values for caffeine content of beverages and foods*

Item	Caffeine content* (mg)
Coffee	
Ground roasted	85 mg/5-oz cup (150 ml)
Instant	60 mg/5-oz cup (150 ml)
Decaffeinated	3 mg/5-oz cup (150 ml)
Tea	
Leaf or bag	30 mg/5-oz cup (150 ml)
Instant	20 mg/5-oz cup (150 ml)
Cola	18 mg/6 oz glass (180 ml)
Caffeine-free colas	0
Cocoa, hot chocolate	4 mg/5 oz-cup (150 ml)
Chocolate milk	4 mg/6-oz glass (180 ml)
Chocolate candy	1.5–6.0 mg/oz (5–20 mg/100 g)

*Barone and Roberts (1996)

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